Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
Sche/II/5/03		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/008169	22.07.2004	26.07.2003

International Patent Classification (IPC) or national classification and IPC

A61K31/135, A61K31/34, A61K31/381 , A61K31/40, A61K31/4164, A61 K31/44, A61P25/24

Applicant

SCHWARZ PHARMA AG

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:

      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/008169

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-14 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* 1-14 received by this Authority on 17.01.2005 with letter of 05.01.2005

nos.* _____ received by this Authority on _____

☒ the drawings:

sheets 1/3-3/3 as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☒ the claims, nos. 13 (in part)

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/008169

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 14 (concerning industrial applicability)

because:

☒ the said international application, or the said claims Nos. 14 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see Supplemental Box

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/008169

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-12, 14	YES
	Claims	13	NO
Inventive step (IS)	Claims		YES
	Claims	1-14	NO
Industrial applicability (IA)	Claims	1-13	YES
	Claims	14	NO

2. Citations and explanations (Rule 70.7)

1. The PCT Contracting States do not have uniform criteria for assessing the industrial applicability of claim 14 in its present form. Patentability may also depend on the wording of the claims. The EPO, for example, does not recognize the industrial applicability of claims to the medical use of a compound; it may, however, allow claims to the first medical application of a known compound or to the use of such a compound in the manufacture of a drug for a new medical application.

2. The present report refers to the following documents:

D1: EP-A-0 334 539 (UPJOHN CO) 27 September 1989 (1989-09-27)

D2: BARTOSZYK G D: "ANXIOLYTIC EFFECTS OF DOPAMINE RECEPTOR LIGANDS: I. INVOLVEMENT OF DOPAMINE AUTORECEPTORS" LIFE SCIENCES, PERGAMON PRESS, OXFORD, GB, Vol. 62, No. 7, 1998, pages 649-663, XP001079854 ISSN: 0024-3205

D3: KOSTOWSKI W ET AL: "5-Hydroxytryptamine(1A)

receptor agonists in animal models of depression and anxiety" PHARMACOLOGY AND TOXICOLOGY 1992 DENMARK, Vol. 71, No. 1, 1992, pages 24-30, XP008039045 ISSN: 0901-9928

D4: DE 198 14 084 A (LOHMANN THERAPIE SYST LTS; DISCOVERY THERAPEUTICS (US)) 14 October 1999 (1999-10-14)

D5: WELNER S A ET AL: "AUTORADIOGRAPHIC QUANTIFICATION OF SEROTONIN-1A RECEPTORS IN RAT BRAIN FOLLOWING ANTIDEPRESSANT DRUG TREATMENT" SYNAPSE (NEW YORK), Vol. 4, No. 4, 1989, pages 347-352, XP008039049 ISSN: 0887-4476

D6: TIMMERMAN, WIA ET AL: "The potential antipsychotic activity of the partial dopamine receptor agonist (+)N-0437" EUROPEAN JOURNAL OF PHARMACOLOGY, 181(3), 253-60 CODEN: EJPHAZ; ISSN: 0014-2999, 1990, XP008039005

D7: US-A-5 214 156 (ANDERSSON BENGT R ET AL) 25 May 1993 (1993-05-25)

D8: PARK S ET AL: "Evaluation of an aminotetraline, CP 14.368, as an antidepressant." CURRENT THERAPEUTIC RESEARCH, CLINICAL AND EXPERIMENTAL. FEB 1972, Vol. 14, No. 2, February 1972 (1972-02), pages 65-70, XP008039025 ISSN: 0011-393X

D9: "Amphetamines", information for professionals: XP8055760.

Novelty

3.1 Document D1 discloses anti-depressant compounds, some of which are encompassed by formula I. R4 can be CH2-phenyl or CH2-thiophene; **R5 = cyclopropyl** (instead of

1-3 alkyl). Examples 17 and 24 disclose the compounds, which are almost encompassed by formula I. Document D2 discloses the compound PPHT*HCl (**N-phenethyl**-N-propylamino-5-hydroxytetralin) (R1=phenethyl instead of heteroarylalkyl), which is a dop+amine agon ist, and the use thereof in anxiety. Tests for the anxiolytic activity of a compound give the same result for PPHT*Hcl as for benzodiazepines.

In document D3 OH-DPAT is described as a $5HT1_a$ agonist, with an anti-depressant and anti-anxiety activity (OH-DPAT: n=3; **R1=H** instead of heteroaryl; R5=Pr; R2=OH; R3, R4=H).

The subject matter of claims 1-12 and 14 is therefore novel over documents D1 to D3 (PCT Article 33(2)).

3.2 In document D6 rotigotine is administered as a dopamine agonist (as a test), together with haloperidol or an amphetamine. Amphetamine inhibits the reuptake of noradrenaline (see document D9, page 2, column 2, paragraph 1) and is encompassed by the scope of protection of claim 13.

The applicant's attention is drawn to the fact that claim 13 was worded as a first medical use (combination preparation), that is to say, the claim relates to a pharmaceutical composition per se. Owing to the wording (first medical use), the use for the treatment of a specific disease/disorder is not considered for the assessment of the claim with regard to novelty. Insofar as claim 13 does not satisfy the requirements of PCT

Article 19(2) and 34(2)(b), the subject matter of claim 13 is not novel over document D6 (PCT Article 33(2)).

Inventive step (EPC Article 56)

4. Should the applicant be able to address the above objections with regard to lack of novelty in order to satisfy the requirements of PCT Article 33, the subject matter of the original claim 13, insofar as it is novel, and of claims 1-12 and 14, further has to satisfy the requirements of PCT Article 33(3), that is to say, involve an inventive step.

Document D1 discloses anti-depressant compounds, some of which are encompassed by formula I. R4 can be CH2-phenyl or CH2-thiophene; **R5 = cyclopropyl** (instead of 1-3 alkyl, see examples 17 and 24).

Document D2 discloses the compound PPHT*HCl (**N-phenethyl**-N-propylamino-5-hydroxytetralin) (R1=phenethyl instead of heteroarylalkyl), which is a dop+amine agonist, and the use thereof in anxiety. Tests for the anxiolytic activity of a compound give the same result for PPHT*HCl as for benzodiazepines.

In document D3 OH-DPAT is described as a $5HT1_a$ agonist, with an anti-depressant and anti-anxiety activity (OH-DPAT: n=3; **R1=H** instead of heteroaryl; R5=Pr; R2=OH; R3, R4=H).

The subject matter of claims 1-14 differs from documents D1 to D3 in that the compounds have a different, but

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

similar structure.

Proceeding from the cited documents D1 to D3, the problem to be solved by the present invention is therefore understood to be that of finding alternative compounds for the treatment of depression.

It would be obvious to a person skilled in the art to use compounds having a structure encompassed by formula I for the treatment of depression: only a single change in their structure would be necessary to prepare the claimed compounds from the compounds of documents D1 to D3.

Consequently, the subject matter of claim 13, insofar as it is novel and satisfies the requirements of PCT Article 19(2) and 34(2)(b), and the subject matter of claims 1-12 and 14, is not inventive (PCT Article 33(3)).

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

Box I

Basis of the report

1. The amendments submitted on 17 January 2005 do not satisfy the requirements of PCT Article 19(2) and 34(2)(b). The basis for the new claim 13 is the original claim 16. However, the specific antipsychotics, sedatives, anxiolytics and migraine preparations specified in claim 13 were never mentioned in the original description. Consequently, the present report was established without taking into consideration the specifically added antipsychotics, sedatives, anxiolytics and migraine preparations.

Box III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1.1 No report is established in respect of aspects of the invention for which no search report was carried out.

2. Claim 14 refers to a subject matter which, in the opinion of the Examining Authority, falls under PCT Rule 67.1(iv). Consequently, no opinion is established with regard to the industrial applicability of this subject matter (PCT Article 34(4)(a)(i)).